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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Bert Vogelstein

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BANNER & WITCOFF

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EXAMINER

BAUGHMAN, MOLLY E

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/828,295

Applicant(s)

VOGELSTEIN ET AL.

Examiner

Molly E. Baughman

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1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 104-108 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 104-108 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/21/04.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☒ Other: Tm Calculations.

Objections/Informalities

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. A critical feature of the claimed invention is molecular beacon probes for use in digital amplification; it is suggested that this be reflected in an amended title.
2. Throughout the specification, the degree symbol and appropriate units should be incorporated. For example, "45°C."
3. Nucleotide sequences of 10 or more bases require Sequence Identifier Numbers (SEQ ID NO:). Such nucleotide sequences are found on page 14 of the specification, example 3.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 105-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 105-106 are confusing because it is cannot be determined what "wild-type nucleic acid" or "mutant nucleic acid" entails. It is unclear whether the probe detects any one nucleic acid within any given sequence, or any one nucleic acid within a selected target sequence, or a certain sequence of nucleic acids within a target

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sequence, or a single target nucleic acid in a sequence complementary to a certain number of nucleic acids within the loop, or a specific sequence of nucleic acids within a target sequence complementary to a certain number of nucleic acids within the loop, etc. Page 16 of the instant specification describes a probe “that would react with WT sequences better than any mutant sequence.” Clarification is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 107 is rejected under 35 U.S.C. 102(a) as anticipated by Marras et al.

Marras et al. teach four molecular beacon probes, each consisting of a 5 base pair stem with sequence 5' –CCACG – 3,' a 16-nucleotide long probe sequence (i.e. loop), and a fluorophore and quencher on opposite ends (page 152, materials and methods). Optimal T_m values for each of the four probes is 56°C (page 153 and 154).

6. Claim 107 is rejected under 35 U.S.C. 102(a) as anticipated by Whitcombe et al.

Whitcombe et al. discuss a molecular beacon probe with a 6 base pair stem consisting of the sequence 5' – CACG – 3' (B2098), which is specific for the C variant of the BRCA2 polymorphism. The loop sequence consists of 17 bases, corresponding to

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a T_m of ~55°C (see T_m calculations), and has a fluorophore on one end of the probe and a quencher flanking the other end (page 807).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 104-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (US 6,037,130).

Tyagi et al. discuss probes of SEQ ID. NO: 1 and 11 (probes 13 and 14), both comprising a stem consisting 5 base pairs comprising the sequence 5' – CCACG – 3'

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and a loop consisting of 15 bases and a T_m of $\sim 57^\circ\text{C}$ (see T_m calculations) and having a photoluminescent dye at the 5' end and DABSYL on the 3' end (column 14, line 63, and column 16, lines 3-55). Probe 14 differs from the nucleotide sequence of Probe 13 by a single nucleotide in the target complement sequence in the loop, and FIG. 17 from this example shows probe 14 was sensitive to a single base-pair mismatch (column 16, lines 40-43).

Regarding claims 104-106, Tyagi et al. do not disclose either of these probes with a stem consisting of only 4 base pairs, nor do they disclose them comprising a loop with a T_m of $50-51^\circ\text{C}$.

Regarding claim 107, Tyagi et al. do not disclose an oligonucleotide beacon probe comprising a loop with a T_m of $54-56^\circ\text{C}$.

Regarding claim 108, Tyagi et al. do not disclose a first oligonucleotide comprising a loop with a T_m of $50-51^\circ\text{C}$, nor a stem consisting of only 4 base pairs. They also do not disclose a second oligonucleotide comprising a loop with a T_m of $54-56^\circ\text{C}$.

One of ordinary skill in the art would have been motivated to optimize the molecular beacon probe of Tyagi et al. to a probe comprising a stem consisting of only 4 base pairs and a loop with a T_m of $50-51^\circ\text{C}$ (claims 104 and 108) or to modify the loop sequence or length of the molecular beacon probe of Tyagi et al. to one with a T_m of $54-56^\circ\text{C}$ because the benefits of routine optimization of molecular beacon probes with more stable, shorter stems and loops with T_m s slightly higher than the annealing temperature to its corresponding target sequence were well known at the time of the

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invention (US 5,925,517). As stated in the MPEP, section 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." As such, the skilled artisan would have had a reasonable expectation of success in modifying the probe of Tyagi et al. through routine optimization to one with a stem having a shorter sequence (4 base pairs), and a loop sequence having a T_m of either 50-51°C or 54-56°C. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to design a molecular beacon probe and use the claimed 4-basepair stem and loop sequence/length with appropriate T_m s therein.

8. Claims 104-106 and 108 are rejected under 35 U.S.C. 103(a) as obvious over Marras et al.

Marras et al. teach four molecular beacon probes, each consisting of a 5 base pair stem with sequence 5' –CCACG – 3,' a 16-nucleotide long probe sequence (i.e. loop), and a fluorophore and quencher on opposite ends (page 152, materials and methods). Optimal T_m values for each of the four probes is 56°C (page 153 and 154).

Furthermore, each of the molecular beacons detects a single nucleotide variant (i.e. A,T,C,or G) at position 1578 of the *Mycobacterium tuberculosis* gene and will not

form a mismatched probe-target hybrid, but fluoresces only when amplification occurs with a perfectly complementary template DNA (page 152 –154).

Regarding claims 104-106, Marras et al. do not discuss a molecular beacon probe consisting of only 4 base pairs, and having a loop with a T_m of 50-51°C.

Regarding claim 108, Marras et al. do not discuss a pair of molecular beacon probes, wherein the first oligonucleotide consists of only 4 base pairs, and has a loop with a T_m of 50-51°C.

One of ordinary skill in the art would have been motivated to optimize the molecular beacon probe of Marras et al. to a probe comprising a stem consisting of only 4 base pairs and a loop with a T_m of 50-51°C (claims 104-106 and 108 in part) because the benefits of optimizing molecular beacon probes with more stable, shorter stems and having loops corresponding to T_m s at which maximum fluorescence occurs when bound to its target sequence in appropriate experimental conditions were well known at the time of the invention, as illustrated by Marras et al. As stated in the MPEP, section 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." As such, the skilled artisan would have had a reasonable expectation of success in optimizing the probe of Marras et al. to one with a stem having a shorter sequence (4 base pairs), and modifying the loop sequence and/or

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length to one having a T_m of 50-51°C. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to design the molecular beacon probe of Marras et al. and use the claimed 4-basepair stem and loop with appropriate T_m s therein.

9. Claims 104-106 and 108 are rejected under 35 U.S.C. 103(a) as obvious over Whitcombe et al.

Whitcombe et al. discuss a molecular beacon probe with a 6 base pair stem consisting of the sequence 5' – CACG – 3' (B2098), which is specific for the C variant of the BRCA2 polymorphism. The loop sequence consists of 17 bases, corresponding to a T_m of ~55°C (see T_m calculations), and has a fluorophore on one end of the probe and a quencher flanking the other end (page 807).

Regarding claims 104-106, Whitcombe et al. do not discuss a molecular beacon probe consisting of only 4 base pairs, and having a loop with a T_m of 50-51°C. They also do not discuss a similar probe that detects a wild-type nucleic acid better than the mutant nucleic acid.

Regarding claim 108, Whitcombe et al. do not discuss a pair of molecular beacon probes, wherein the first oligonucleotide consists of only 4 base pairs, and has a loop with a T_m of 50-51°C.

One of ordinary skill in the art would have been motivated to optimize the molecular beacon probe of Whitcombe et al. to a probe that detects a wild-type nucleic acid better than a mutant nucleic acid, comprising a stem consisting of only 4 base pairs

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and a loop with a T_m of 50-51°C (claims 104-106 and 108 in part) because the benefits of designing molecular beacon probes with more stable, shorter stems and having loops corresponding to T_m s at which maximum fluorescence occurs through routine optimization were well known at the time of the invention, as illustrated by Marras et al. As stated in the MPEP, section 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." As such, the skilled artisan would have had a reasonable expectation of success in modifying the probe of Whitcombe et al. to one with a stem having a shorter sequence (4 base pairs), and modifying the loop sequence and/or length to one having a T_m of 50-51°C. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to optimize the molecular beacon probe of Whitcombe et al. with the claimed 4-basepair stem and loop sequence/length with appropriate T_m s therein.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

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are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 104-108 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-37 of U.S. Patent No. 6,440,706. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent and instant claims have a genus:species relationship. For example, in claim 33 of US 6,440,706, the loop of the molecular beacon comprises 16 bases and claim 104 of the instant invention comprises a loop consisting of 14-26 bases. Claim 107 of the instant invention requires a loop consisting of 14-26 bases and a stem consisting of 4-6 base pairs, whereas the patent claim requires a loop consisting of 19-20 base pairs, and a stem consisting of 4 base pairs. Therefore, the instant claims are obvious in the view of the patent claims since they relate as species and genus, respectively.

11. No claims are free of the prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 8/18/06

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

8/21/06